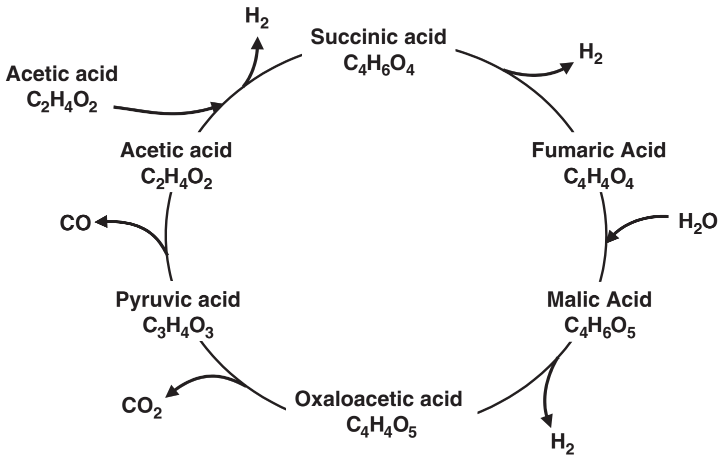

Figure 3.14. Cycle of reactions proposed by Thunberg.

citric acid combining to form succinic acid, Krebs proposed that oxaloacetic acid combined with a three-carbon substance that Krebs temporarily called *triose* to generate citric acid, with the citric acid then undergoing a sequence of reactions resulting in succinic acid (Krebs & Johnson, 1937). (See center part of Figure 3.15.) It was soon realized that pyruvic acid (pyruvate), a product at the end of glycolysis, provided the material that would react with oxaloacetic acid. Figuring out the exact linkage provided a bit of a challenge. After Fritz Lippman (1945) discovered coenzyme A, evidence began to develop that it figured in the connection. Feodor Lynen initiated research attempting to show that acetic acid figured in the pathway between pyruvic acid and citric acid, but because ordinary acetic acid would not condense with oxalacetic acid to create citric acid, he speculated that *activated acetic acid* must be involved. Lynen and Richert (1951) demonstrated that the activated acetic acid was a thio (sulfur) ester of acetylated coenzyme A, a compound now known as acetyl-CoA. With this account of the connection, the citric acid cycle was linked to the pathway of glycolysis (as well as the pathways of fatty acid metabolism and protein metabolism).

Another key advance, working from the oxygen end of the overall process, came from a very unlikely source. David Keilin was studying the respiration of the parasite horse bot-fly (*Gasterophilus intestinalis*), when he detected a disappearance of hemoglobin in later stages of metamorphosis from the pupa to adult fly stage. Spectroscopic examination of flies that died in captivity revealed a pigment with four distinct absorption bands. Keilin considered the possibility that the pigment originated from the larval hemoglobin,

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